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=> s (Farb, D? or Farb D?)/au
            57 FARB, D?/AU
            57 FARB D?/AU
L12         57 (FARB, D? OR FARB D?)/AU

=> d his

     (FILE 'HOME' ENTERED AT 12:19:39 ON 05 NOV 2001)

     FILE 'MEDLINE' ENTERED AT 12:19:48 ON 05 NOV 2001
                SET PLURALS ON PERM
L1          11420 S NMDA RECEPTOR
L2              0 S SUBUNIT SPECIFIC MODULATOR
L3            120 S STEROID MODULATION
L4              1 S L1 AND L3
L5            801 S NR1 OR NR2
L6            570 S L1 AND L5
L7             12 S STEROID MODULATOR
L8              0 S L6 AND L7
L9              0 S SUBUNIT SPECIFIC MODULATOR
L10             0 S NR1 MODULATOR
L11             0 S NR2 MODULATOR
L12            57 S (FARB, D? OR FARB D?)/AU

=> s L1 and L12
L13             8 L1 AND L12

=> d 1-8 L13 ti au so abs

L13  ANSWER 1 OF 8     MEDLINE
TI   Geometry and charge determine pharmacological effects of steroids on
     N-methyl-D-aspartate receptor-induced Ca(2+) accumulation and cell death.
AU   Weaver C E; Land M B; Purdy R H; Richards K G; Gibbs T T; Farb D H
SO   JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (2000 Jun) 293 (3)
     747-54.
     Journal code: JP3; 0376362. ISSN: 0022-3565.
AB   Modulation of N-methyl-D-aspartate (NMDA) receptor
     function by a series of sulfated steroids and dicarboxylic acid ester
     analogs of pregnenolone sulfate and pregnanolone sulfate was investigated
     in cultured hippocampal neurons. The "bent" steroid ring structure
     associated with 5beta-stereochemistry favors receptor inhibition, whereas
     the more planar ring structure of the pregn-5-enes and 5alpha-pregnanes
     favors potentiation of NMDA-induced [Ca(2+)] increases and neuronal cell
     death. The nature of the negatively charged group attached to the steroid
     C3 position is important for both the neuroprotection afforded by pregnane
     steroids and the exacerbation of NMDA-induced neuronal death by
     pregn-5-enes. Dicarboxylic acid hemiesters of various lengths can
     substitute for the sulfate group of the positive modulator pregnenolone
     sulfate and the negative modulator pregnanolone sulfate. This result
     suggests that precise coordination with the oxygen atoms of the sulfate
     group is not critical for modulation and that the steroid recognition
     sites can accommodate bulky substituents at C3. The capacity of charged
     steroids to enhance or protect against NMDA-induced death of hippocampal
     neurons is strongly correlated with modulation of NMDA-induced Ca(2+)
     accumulation, indicating that direct enhancement or inhibition of
     NMDA receptor function is responsible for the
     proexcitotoxic or neuroprotective effects of these steroids.

L13  ANSWER 2 OF 8     MEDLINE
TI   Neurosteroid modulation of recombinant ionotropic glutamate receptors.
AU   Yaghoubi N; Malayev A; Russek S J; Gibbs T T; Farb D H
SO   BRAIN RESEARCH, (1998 Aug 24) 803 (1-2) 153-60.
     Journal code: B5L; 0045503. ISSN: 0006-8993.
AB   Pregnenolone sulfate (PS) is an abundant neurosteroid that can potentiate
     or inhibit ligand gated ion channel activity and thereby alter neuronal
     excitability. Whereas PS is known to inhibit kainate and AMPA responses
     while potentiating NMDA responses, the dependence of modulation on
     receptor subunit composition remains to be determined. Toward this end,
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the effect of PS on recombinant kainate (GluR6), AMPA (GluR1 or GluR3), and NMDA (NR1(100)+NR2A) receptors was characterized electrophysiologically with respect to efficacy and potency of modulation. With Xenopus oocytes expressing GluR1, GluR3 or GluR6 receptors, PS reduces the efficacy of kainate without affecting its potency, indicative of a noncompetitive mechanism of action. Conversely, with oocytes expressing NR1(100)+NR2A subunits, PS enhances the efficacy of NMDA without affecting its potency. Whereas the modulatory efficacy, but not the potency, of PS is increased two-fold by co-injection of NR1(100)+NR2A cRNAs as compared with NR1(100) cRNA alone, there is little or no effect of the NR2A subunit on efficacy or potency of pregnanolone (or epipregnanolone) sulfate as an inhibitor of the NMDA response. This suggests that the NR2A subunit controls the efficacy of neurosteroid enhancement, but not inhibition, which is consistent with our previous finding that potentiating and inhibitory steroids act at distinct sites on the **NMDA receptor**. This represents a first step towards understanding the role of subunit composition in determining neurosteroid modulation of ionotropic glutamate receptor function.

L13 ANSWER 3 OF 8 MEDLINE
TI Distinct sites for inverse modulation of N-methyl-D-aspartate receptors by sulfated steroids.
AU Park-Chung M; Wu F S; Purdy R H; Malayev A A; Gibbs T T; **Farb D H**
SO MOLECULAR PHARMACOLOGY, (1997 Dec) 52 (6) 1113-23.
Journal code: NGR; 0035623. ISSN: 0026-895X.
AB Steroid sulfation occurs in nervous tissue and endogenous sulfated steroids can act as positive or negative modulators of N-methyl-D-aspartate (**NMDA**) **receptor** function. In the current study, structure-activity relationships for sulfated steroids were examined in voltage-clamped chick spinal cord and rat hippocampal neurons in culture and in Xenopus laevis oocytes expressing NR1(100) and NR2A subunits. The ability of pregnenolone sulfate (a positive modulator) and epipregnanolone sulfate (a negative modulator) to compete with each another, as well as with other known classes of **NMDA receptor** modulators, was examined. The results show that steroid positive and negative modulators act at specific, extracellularly directed sites that are distinct from one another and from the spermine, redox, glycine, Mg2+, MK-801, and arachidonic acid sites. Sulfated steroids are effective as modulators of ongoing glutamate-mediated synaptic transmission, which is consistent with their possible role as endogenous neuromodulators in the CNS.

L13 ANSWER 4 OF 8 MEDLINE
TI Neuroprotective activity of a new class of steroidal inhibitors of the N-methyl-D-aspartate receptor.
AU Weaver C E Jr; Marek P; Park-Chung M; Tam S W; **Farb D H**
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1997 Sep 16) 94 (19) 10450-4.
Journal code: PV3; 7505876. ISSN: 0027-8424.
AB Release of the excitatory neurotransmitter glutamate and the excessive stimulation of N-methyl-D-aspartate (NMDA)-type glutamate receptors is thought to be responsible for much of the neuronal death that occurs following focal hypoxia-ischemia in the central nervous system. Our laboratory has identified endogenous sulfated steroids that potentiate or inhibit NMDA-induced currents. Here we report that 3alpha-ol-5beta-pregnan-20-one hemisuccinate (3alpha5betaHS), a synthetic homologue of naturally occurring pregnanolone sulfate, inhibits NMDA-induced currents and cell death in primary cultures of rat hippocampal neurons. 3alpha5betaHS exhibits sedative, anticonvulsant, and analgesic properties consistent with an action at NMDA-type glutamate receptors. Intravenous administration of 3alpha5betaHS to rats (at a nonsedating dose) following focal cerebral ischemia induced by middle cerebral artery occlusion significantly reduces cortical and subcortical infarct size. The in vitro and in vivo neuroprotective effects of 3alpha5betaHS demonstrate that this steroid represents a new class of potentially useful therapeutic agents for the treatment of stroke and certain neurodegenerative diseases that involve over activation of **NMDA receptors**.

L13 ANSWER 5 OF 8 MEDLINE
TI 17beta-Estradiol protects against NMDA-induced excitotoxicity by direct inhibition of **NMDA receptors**.
AU Weaver C E Jr; Park-Chung M; Gibbs T T; **Farb D H**
SO BRAIN RESEARCH, (1997 Jul 4) 761 (2) 338-41.
Journal code: B5L; 0045503. ISSN: 0006-8993.
AB Several lines of evidence suggest that 17beta-estradiol (betaE2) has neuroprotective properties. The risk and severity of dementia are decreased in women who have received estrogen therapy, and betaE2 protects neurons in vitro against death from a variety of stressors. Neuroprotection by betaE2 has been suggested to be due to free radical scavenging. We demonstrate an additional neuroprotective mechanism whereby betaE2 protects against NMDA-induced neuronal death by directly inhibiting the **NMDA receptor**.

L13 ANSWER 6 OF 8 MEDLINE
TI 3 alpha-Hydroxy-5 beta-pregnan-20-one sulfate: a negative modulator of the NMDA-induced current in cultured neurons.
AU Park-Chung M; Wu F S; **Farb D H**
SO MOLECULAR PHARMACOLOGY, (1994 Jul) 46 (1) 146-50.
Journal code: NGR; 0035623. ISSN: 0026-895X.
AB We have shown previously that the neurosteroid pregnenolone sulfate acts as a positive allosteric modulator at the N-methyl-D-aspartate (**NMDA**) **receptor** while inhibiting the kainate, the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA), the glycine, and the gamma-aminobutyric acid (GABA) responses of chick spinal cord neurons. Here, we report that 3 alpha-hydroxy-5 beta-pregnan-20-one sulfate (5 beta 3 alpha S), a sulfated form of naturally occurring 5 beta 3 alpha, inhibits both the NMDA and the non-**NMDA receptor**-mediated responses as measured by whole cell voltage clamp recordings. 100 microM 5 beta 3 alpha S rapidly and reversibly inhibits the response to 30 microM NMDA by 66%, 50 microM kainate by 37%, and 25 microM AMPA by 29%. Application of 50 microM nonsulfated 5 beta 3 alpha does not produce any significant effect on the NMDA response, demonstrating that the sulfate moiety is important for the effect of 5 beta 3 alpha S on the NMDA response. The effect of 5 beta 3 alpha S on the NMDA response is concentration dependent, with an EC50 of 62 microM. 5 beta 3 alpha S reduces the maximum NMDA response with little effect on the NMDA EC50, indicating that antagonism of the NMDA response by 5 beta 3 alpha S is noncompetitive. The fact that 5 beta 3 alpha S inhibition of the NMDA response is neither agonist nor voltage dependent demonstrates that 5 beta 3 alpha S does not act as an open channel blocker. Furthermore, inhibition of the NMDA response by 5 beta 3 alpha S is not reduced by the addition of a maximal concentration (10 microM) of glycine, indicating that 5 beta 3 alpha S does not act via the glycine recognition site. The inhibitory action of 5 beta 3 alpha S on the NMDA and non-**NMDA receptors** may provide a basis for inhibiting glutamate receptor-induced seizures and excitotoxic cell death.

L13 ANSWER 7 OF 8 MEDLINE
TI Pregnenolone sulfate augments **NMDA receptor** mediated increases in intracellular Ca2+ in cultured rat hippocampal neurons.
AU Irwin R P; Maragakis N J; Rogawski M A; Purdy R H; **Farb D H**; Paul S M
SO NEUROSCIENCE LETTERS, (1992 Jul 6) 141 (1) 30-4.
Journal code: N7N; 7600130. ISSN: 0304-3940.
AB The ability of the neuroactive steroid pregnenolone sulfate to alter N-methyl-D-aspartate (**NMDA**) **receptor**-mediated elevations in intracellular Ca2+ ([Ca2+]i) was studied in cultured fetal rat hippocampal neurons using microspectrofluorimetry and the Ca2+ sensitive indicator fura-2. Pregnenolone sulfate (5-250 microM) caused a concentration-dependent and reversible potentiation of the rise (up to approximately 800%) in [Ca2+]i induced by NMDA. In contrast, the steroid failed to alter basal (unstimulated) [Ca2+]i or to modify the rise in [Ca2+]i that occurs when hippocampal neurons are depolarized by high K+ in the presence of the **NMDA receptor** antagonist CPP. These data suggest that the previously reported excitatory properties of

pregnenolone sulfate may be due, in part, to an augmentation of the action of glutamic acid at the **NMDA receptor**.

L13 ANSWER 8 OF 8 MEDLINE
TI Pregnenolone sulfate: a positive allosteric modulator at the N-methyl-D-aspartate receptor.
AU Wu F S; Gibbs T T; **Farb D H**
SO MOLECULAR PHARMACOLOGY, (1991 Sep) 40 (3) 333-6.
Journal code: NGR; 0035623. ISSN: 0026-895X.
AB The N-methyl-D-aspartate (**NMDA**) **receptor** is believed to play a major role in learning and in excitotoxic neuronal damage associated with stroke and epilepsy. Pregnenolone sulfate, a neurosteroid, specifically enhances NMDA-gated currents in spinal cord neurons, while inhibiting receptors for the inhibitory amino acids glycine and gamma-aminobutyric acid, as well as non-NMDA glutamate receptors. This observation is consistent with the hypothesis that neurosteroids such as pregnenolone sulfate are involved in regulating the balance between excitation and inhibition in the central nervous system.

FILE 'MEDLINE' ENTERED AT 12:1[redacted]8 ON 05 NOV 2001
SET PLURALS ON TERM
L1 11420 S NMDA RECEPTOR
L2 0 S SUBUNIT SPECIFIC MODULATOR
L3 120 S STEROID MODULATION
L4 1 S L1 AND L3
L5 801 S NR1 OR NR2
L6 570 S L1 AND L5
L7 12 S STEROID MODULATOR
L8 0 S L6 AND L7
L9 0 S SUBUNIT SPECIFIC MODULATOR
L10 0 S NR1 MODULATOR
L11 0 S NR2 MODULATOR

=> d L7 ti au so abs

L7 ANSWER 1 OF 12 MEDLINE
TI Melatonin potentiates the GABA(A) receptor-mediated current in cultured chick spinal cord neurons.
AU Wu F S; Yang Y C; Tsai J J
SO NEUROSCIENCE LETTERS, (1999 Feb 5) 260 (3) 177-80.
Journal code: N7N; 7600130. ISSN: 0304-3940.
AB The effect of melatonin on the gamma-aminobutyric acidA (GABA(A)) receptor-mediated response was studied in cultured chick spinal cord neurons using the whole-cell voltage-clamp recording technique. Melatonin rapidly and reversibly potentiated the GABA-induced current in a dose-dependent fashion, with an EC50 of 766 microM and a maximal potentiation of 148%. Potentiation of the GABA response by melatonin was mediated by increasing the potency of GABA rather than the efficacy. Prolonged exposure to a saturating concentration of the disulfide-reducing agent dithiothreitol did not attentuate the effect of melatonin on the GABA response, indicating that melatonin does not act through the redox site. Furthermore, our results demonstrate that melatonin and 5alpha-pregnan-3alpha-ol-20-one (a positive **steroid modulator** of the GABA(A) receptor) act through different sites.

=> d 2-12 ti au so abs
L11 HAS NO ANSWERS
L11 0 SEA FILE=MEDLINE PLU=ON NR2 MODULATOR

=> d 2-12 L7 ti au so abs

L7 ANSWER 2 OF 12 MEDLINE
TI Ganaxolone, a selective, high-affinity **steroid modulator** of the gamma-aminobutyric acid-A receptor, exacerbates seizures in animal models of absence.
AU Snead O C 3rd
SO ANNALS OF NEUROLOGY, (1998 Oct) 44 (4) 688-91.
Journal code: 6AE; 7707449. ISSN: 0364-5134.
AB Ganaxolone (3alpha-hydroxy-3beta-methyl-5alpha-pregnan-20-one) is a novel neurosteroid which has anticonvulsant properties in a number of seizure models as well as the ability to enhance function of the gamma-aminobutyric acid-A (GABA(A)) receptor complex via a neurosteroid binding site. The object of these experiments was to ascertain the efficacy of ganaxolone against absence seizures. Ganaxolone was assessed in the low-dose pentylenetetrazol (PTZ) and the gamma-hydroxybutyric acid (GHB) model of absence seizures in rats. Ganaxolone pretreatment resulted in a significant prolongation of absence seizure in both the PTZ and GHB models. Further, ganaxolone in doses above 20 mg/kg alone produced bilaterally synchronous spike wave discharges (SWDs) associated with behavioral arrest. These data suggest that augmentation of GABA(A) receptor complex function by neurosteroids has the potential to result in or exacerbate absence seizures.

L7 ANSWER 3 OF 12 MEDLINE
TI Substituted 3beta-phenylethynyl derivatives of 3alpha-hydroxy-5alpha-

pregnan-20-one: remarkable potent neuroactive **steroid modulators** of gamma-aminobutyric acidA receptors.

AU Hawkinson J E; Acosta-Burruel M; Yang K C; Hogenkamp D J; Chen J S; Lan N C; Drewe J A; Whittemore E R; Woodward R M; Carter R B; Upasani R B

SO JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (1998 Oct) 287 (1) 198-207.
Journal code: JP3; 0376362. ISSN: 0022-3565.

AB Neuroactive steroids are positive allosteric modulators of gamma-aminobutyric acidA (GABAA) receptor complexes. Synthetic modification generally does not increase neuroactive steroid potency beyond that of the naturally occurring progesterone metabolite, 3alpha-hydroxy-5alpha-pregnan-20-one (3alpha,5alpha-P). Recently, it has been shown that introduction of appropriately para-substituted phenylethynyl groups at the 3beta-position of 5beta steroids increases receptor potency. The present report presents the synthesis and pharmacological profile of an analogous series of 5alpha steroids. The most striking feature of this series is the further enhancement of in vitro and in vivo potency obtained. In particular, 3beta-(p-acetylphenylethynyl)-3alpha-hydroxy-5alpha-pr egnan-20-one (Co 152791) was 11-, 16- and 49-fold more potent than 3alpha, 5alpha-P in modulating the binding of [35S]TBPS, [3H]flunitrazepam and [3H]muscimol, respectively, in rat brain membranes (Co 152791 IC50 or EC50 = 2-7.5 nM). Similarly, Co 152791 was 3- to 20-fold more potent than 3alpha,5alpha-P as an inhibitor of [35S]TBPS binding in human recombinant receptor combinations containing alpha1, alpha2, alpha3 or alpha5 and beta2gamma2L subunits (Co 152791 IC50 1.4-5.7 nM). Co 152791 displayed low efficacy and 3alpha,5alpha-P had low potency at alpha4/6beta3gamma2L GABAA receptor complexes. Interestingly, Co 152791 demonstrated remarkable potency as a potentiator of GABA-evoked currents in Xenopus oocytes expressing alpha1beta2gamma2L receptors (EC50 0.87 nM), being 184-fold more potent than 3alpha,5alpha-P. High in vitro potency was also reflected in enhanced in vivo activity in that Co 152791 exhibited exceptional anticonvulsant potency, protecting mice from pentylenetetrazol-induced seizures at a approximately 5-fold lower dose than 3alpha,5alpha-P after i.p. administration (Co 152791 ED50 0.6 mg/kg). Moreover, Co 152791 was orally active (ED50 1.1 mg/kg) and exhibited a therapeutic index of 7 relative to rotorod impairment. The remarkable potency of Co 152791 as a positive allosteric modulator of GABAA receptors may be explained by its interaction with an auxiliary binding pocket in the neuroactive steroid binding site. In addition, modification at the 3beta-position probably hinders metabolism of the 3alpha-hydroxy group contributing to the exceptional anticonvulsant potency of this compound relative to other neuroactive steroids.

L7 ANSWER 4 OF 12 MEDLINE

TI Binding of **steroid modulators** to recombinant cytosolic domain from mouse P-glycoprotein in close proximity to the ATP site.

AU Dayan G; Jault J M; Baubichon-Cortay H; Baggetto L G; Renoir J M; Baulieu E E; Gros P; Di Pietro A

SO BIOCHEMISTRY, (1997 Dec 9) 36 (49) 15208-15.
Journal code: A0G; 0370623. ISSN: 0006-2960.

AB We recently found that recombinant NBD1 cytosolic domain corresponding to segment 395-581 of mouse mdr1 P-glycoprotein bound fluorescent 2'(3')-N-methylanthraniloyl-ATP (MANT-ATP) with high affinity [Dayan, G., Baubichon-Cortay, H., Jault, J.-M., Cortay, J. -C., Deleage, G., & Di Pietro, A. (1996) J. Biol. Chem. 271, 11652-11658]. The present work shows that a longer 371-705 domain (extended-NBD1), including tryptophan-696 as an intrinsic probe, which bound MANT-ATP with identical affinity, also interacted with steroids known to modulate anticancer drug efflux from P-glycoprotein-positive multidrug-resistant cells. Progesterone, which is not transported, its hydrophobic derivatives medroxyprogesterone acetate and megestrol acetate, and Delta6-progesterone produced nearly a 50% saturating quenching of the domain intrinsic fluorescence, with dissociation constants ranging from 53 to 18 microM. The even more hydrophobic antiprogestin RU 486 produced a complete quenching of tryptophan-696 fluorescence, in contrast to more hydrophilic derivatives of progesterone containing hydroxyl groups at positions 11, 16, 17, and 21 and known to be transported, which produced very little quenching. A similar differential interaction was observed with full-length purified

P-glycoprotein. The stero[redacted]binding region within extended[redacted]D1 appeared distinct from the nucleotide-binding site as the RU 486-induced quenching was neither prevented nor reversed by high ATP concentrations. In contrast, MANT-ATP binding was efficiently prevented or displaced by RU 486, suggesting that the hydrophobic MANT group of the bound nucleotide analogue overlaps, at least partially, the adjacent steroid-binding region revealed by RU 486.

L7 ANSWER 5 OF 12 MEDLINE
TI Characterization of the anticonvulsant properties of ganaxolone (CCD 1042; 3alpha-hydroxy-3beta-methyl-5alpha-pregnan-20-one), a selective, high-affinity, **steroid modulator** of the gamma-aminobutyric acid(A) receptor.
AU Carter R B; Wood P L; Wieland S; Hawkinson J E; Belelli D; Lambert J J; White H S; Wolf H H; Mirsadeghi S; Tahir S H; Bolger M B; Lan N C; Gee K W
SO JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (1997 Mar) 280 (3) 1284-95.
Journal code: JP3; 0376362. ISSN: 0022-3565.
AB Ganaxolone (CCD 1042) is a 3beta-methyl-substituted analog of the endogenous neuroactive steroid 3alpha-hydroxy-5alpha-pregnan-20-one. Ganaxolone inhibited binding of the gamma-aminobutyric acid (GABA)A receptor-chloride channel ligand t-[35S]butylbicyclophosphorothionate (IC50 of 80 nM) and enhanced binding of the benzodiazepine site ligand [3H]flunitrazepam (EC50 of 125 nM) and the GABA site ligand [3H]muscimol (EC50 of 86 nM), consistent with activity as a positive allosteric modulator of the GABA(A) receptor. Electrophysiological recordings showed that, whereas nanomolar concentrations of ganaxolone potentiated GABA-evoked chloride currents in Xenopus oocytes expressing the human GABA(A) receptor subunits alpha1beta1gamma2L, alpha2beta1gamma2L or alpha3beta1gamma2L, direct activation of chloride flux occurred to a limited extent only at micromolar concentrations. Ganaxolone was effective in nontoxic doses against clonic convulsions induced by s.c. pentylenetetrazol administration in mice and rats (ED50 values of 4.3 and 7.8 mg/kg i.p., respectively). Ganaxolone also exhibited potent anticonvulsant activity against seizures induced by s.c. bicuculline (ED50 of 4.6 mg/kg i.p.), i.p. TBPS (ED50 of 11.7 mg/kg i.p.) and i.p. aminophylline (ED50 of 11.5 mg/kg i.p.) in mice. Although ganaxolone effectively blocked tonic seizures induced by maximal electroshock in mice (ED50 of 29.7 mg/kg i.p.), it did so only at doses that produced ataxia on the Rotorod (TD50 of 33.4 mg/kg i.p.). Conversely, ganaxolone was a potent anticonvulsant against fully kindled stage 5 seizures induced by corneal kindling in rats (ED50 of 4.5 mg/kg i.p.), producing these effects at doses well below those that resulted in ataxia (TD50 of 14.2 mg/kg i.p.). The seizure threshold, as determined by an increase in the dose of i.v. infused pentylenetetrazol required to induce clonus, was also significantly elevated by nontoxic doses of ganaxolone in mice. In summary, these data indicate that ganaxolone is a high-affinity, stereoselective, positive allosteric modulator of the GABA(A) receptor complex that exhibits potent anticonvulsant activity across a range of animal procedures. The profile of anticonvulsant activity obtained for ganaxolone supports clinical evaluation of this drug as an antiepileptic therapy with potential utility in the treatment of generalized absence seizures as well as simple and complex partial seizures.

L7 ANSWER 6 OF 12 MEDLINE
TI Synthesis and in vitro activity of 3 beta-substituted-3 alpha-hydroxypregnan-20-ones: allosteric modulators of the GABAA receptor.
AU Hogenkamp D J; Tahir S H; Hawkinson J E; Upasani R B; Alauddin M; Kimbrough C L; Acosta-Burruel M; Whittemore E R; Woodward R M; Lan N C; Gee K W; Bolger M B
SO JOURNAL OF MEDICINAL CHEMISTRY, (1997 Jan 3) 40 (1) 61-72.
Journal code: J0F; 9716531. ISSN: 0022-2623.
AB Two naturally occurring metabolites of progesterone, 3 alpha-hydroxy-5 alpha- and 5 beta-pregnan-20-one (1 and 2), are potent allosteric modulators of the GABAA receptor. Their therapeutic potential as anxiolytics, anticonvulsants, and sedative/hypnotics is limited by rapid metabolism. To avoid these shortcomings, a series of 3 beta-substituted derivatives of 1 and 2 was prepared. Small lipophilic groups generally

maintain potency in both [redacted] 5 alpha- and 5 beta-series as [redacted]termined by inhibition of [35S]TBPS binding. In the 5 alpha-series, 3 beta-ethyl, -propyl, -trifluoromethyl and -(benzyloxy)methyl, as well as substituents of the form 3 beta-XCH2, where X is Cl, Br, or I or contains unsaturation, show limited efficacy in inhibiting [35S]TBPS binding. In the 5 beta-series, the unsubstituted parent 2 is a two-component inhibitor, whereas all of the 3 beta-substituted derivatives of 2 inhibit TBPS via a single class of binding sites. In addition, all of the 3-substituted 5 beta-sterols tested are full inhibitors of [35S]TBPS binding. Electrophysiological measurements using alpha 1 beta 2 gamma 2L receptors expressed in oocytes show that 3 beta-methyl- and 3 beta-(azidomethyl)-3 alpha-hydroxy-5 alpha-pregnan-20-one (6 and 22, respectively) are potent full efficacy modulators and that 3 alpha-hydroxy-3 beta-(trifluoromethyl)-5 alpha-pregnan -20-one (24) is a low-efficacy modulator, confirming the results obtained from [35S]TBPS binding. These results indicate that modification of the 3 beta-position in 1 and 2 maintains activity at the neuroactive steroid site on the GABAA receptor. In animal studies, compound 6 (CCD 1042) is an orally active anticonvulsant, while the naturally occurring progesterone metabolites 1 and 2 are inactive when administered orally, suggesting that 3 beta-substitution slows metabolism of the 3-hydroxyl, resulting in orally bioavailable **steroid modulators** of the GABAA receptor.

L7 ANSWER 7 OF 12 MEDLINE
TI Neurosteroid analogues. 4. The effect of methyl substitution at the C-5 and C-10 positions of neurosteroids on electrophysiological activity at GABAA receptors.
AU Han M; Zorumski C F; Covey D F
SO JOURNAL OF MEDICINAL CHEMISTRY, (1996 Oct 11) 39 (21) 4218-32.
Journal code: J0F; 9716531. ISSN: 0022-2623.
AB A series of analogues of the neuroactive steroids 3 alpha-hydroxy-5 alpha-pregnan-20-one and 3 alpha-hydroxy-5 beta-pregnan-20-one were studied to elucidate the mode of binding of 5 alpha-and 5 beta-reduced steroids to steroid binding sites on GABAA receptors. Analogues which were either 3 alpha-hydroxy-20-ketosteroids or 3 alpha-hydroxysteroid-17 beta-carbonitriles and which contained various methyl group substitution patterns at C-5 and C-10 were prepared. Evaluations utilized whole-cell patch clamp electrophysiological methods carried out on cultured rat hippocampal neurons, and the results obtained with the rigid 17 beta-carbonitrile analogs were analyzed using molecular modeling methods. The molecular modeling results provide a rationale for the observation that the configuration of the hydroxyl group at C-3 is a greater determinant of anesthetic potency than the configuration of the A,B ring fusion at C-5. The electrophysiological results identify steric restrictions for the space that can be occupied in 5 alpha- and 5 beta-reduced **steroid modulators** of GABAA receptors in the regions of space proximate to the steroid C-5, C-10, and possibly C-4 positions. This information is useful for the development of nonsteroidal analogues that can modulate GABAA receptors via interactions at steroid binding sites.

L7 ANSWER 8 OF 12 MEDLINE
TI Neuroactive **steroid modulators** of the stress response.
AU Morrow A L; Devaud L L; Purdy R H; Paul S M
SO ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, (1995 Dec 29) 771 257-72.
Ref: 78
Journal code: 5NM; 7506858. ISSN: 0077-8923.

L7 ANSWER 9 OF 12 MEDLINE
TI Dual activation of GABAA and glycine receptors by beta-alanine: inverse modulation by progesterone and 5 alpha-pregnan-3 alpha-ol-20-one.
AU Wu F S; Gibbs T T; Farb D H
SO EUROPEAN JOURNAL OF PHARMACOLOGY, (1993 Aug 15) 246 (3) 239-46.
Journal code: EN6; 1254354. ISSN: 0014-2999.
AB The differential sensitivity of the glycine and GABAA receptors to modulation by progesterone and 5 alpha-pregnan-3 alpha-ol-20-one (5 alpha 3 alpha) was used to determine whether beta-alanine acts through its own receptor, or through the glycine and/or GABAA receptor(s). The response to

beta-alanine resembles th[redacted]lycine response as it is inhib[redacted]d by strychnine (a competitive glycine antagonist) or progesterone (a negative modulator of the glycine response). Significantly, the response to beta-alanine also resembles the GABA response in that it is inhibited by 2-(carboxy-3'-propyl)-3-amino-6-paramethoxy-phenylpyridazinium+ ++ bromide (SR-95531; a competitive GABA antagonist) and potentiated by 5 alpha 3 alpha (a positive modulator of the GABA response). The efficacy of beta-alanine at the GABAA receptor is comparable to that of GABA. Similarly, the efficacy of beta-alanine at the glycine receptor is comparable to that of glycine. The greater potency of beta-alanine at the glycine receptor indicates that, if beta-alanine is a neurotransmitter, its effects are more likely to be mediated by glycine receptors than by GABAA receptors. However, activation of the GABAA receptor by beta-alanine may become important in the presence of **steroid modulators** such as progesterone or 5 alpha 3 alpha.

L7 ANSWER 10 OF 12 MEDLINE
TI Steroid anesthetics and naturally occurring analogs modulate the gamma-aminobutyric acid receptor complex at a site distinct from barbiturates.
AU Turner D M; Ransom R W; Yang J S; Olsen R W
SO JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (1989 Mar) 248 (3) 960-6.
Journal code: JP3; 0376362. ISSN: 0022-3565.
AB The steroid anesthetic alphaxalone and a series of naturally occurring analogs were compared in potency and efficacy with each other and the hypnotic barbiturate pentobarbital for interaction with gamma-aminobutyric acid (GABA) receptors:binding sites in rat brain membranes and functional activity in 36Cl- flux measurements with rat hippocampal slices. The steroids enhanced [3H]muscimol binding to GABA receptor sites, enhanced [3H] flunitrazepam binding to benzodiazepine receptors and inhibited [35S]t-butyl bicyclophosphorothionate binding to picrotoxin/convulsant binding sites on the GABA receptor-chloride channel complex. The same steroids that were active in modulating the binding of ligands to the various receptor sites on the GABA receptor complex at micromolar concentrations enhanced muscimol-stimulated 36Cl- flux in rat hippocampal slices. The steroids, like the barbiturates, increased the maximal response to muscimol but produced little or no potentiation of basal 36Cl- flux in the absence of GABA agonist. Although the effects of steroids and barbiturates were similar, separate sites of action were demonstrated conclusively by the observation that the two classes of compounds, when included together, gave additive or synergistic effects on binding, as well as on 36Cl- flux in the absence of GABA agonist. Structure-activity studies showed that the synthetic steroid anesthetic alphaxalone was the most potent compound tested, followed by the naturally occurring steroids tetrahydro-deoxycorticosterone, allo-tetrahydrocorticosterone, cis-androsterone and 5 alpha-androstan-17 beta-ol-3-one. The ability of several naturally occurring steroids to enhance GABA-mediated inhibition in the brain suggests the possibility of an endogenous **steroid modulator** of neuronal function.

L7 ANSWER 11 OF 12 MEDLINE
TI Effect of estradiol and progesterone on human chorionic gonadotropin secretion in vitro.
AU Wilson E A; Jawad M J; Powell D E
SO AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, (1984 May 15) 149 (2) 143-8.
Journal code: 3NI; 0370476. ISSN: 0002-9378.
AB Many of the substances known to control the secretion of pituitary gonadotropins also modulate the secretion of human chorionic gonadotropin (hCG) by the placenta. In order to study the effect of estrogens and progestins on hCG secretion, term placental explants were cultured in culture media for 144 hours. During the culture period, hCG secretion increased after 48 hours, and a fortyfold increase was observed after 144 hours (p less than 0.001). Compared to concentrations of hCG in control cultures, secretion of hCG was markedly suppressed in the presence of progesterone 2.25 X 10(-5)M (p less than 0.001), a concentration similar to that found in term placental tissue (1.7 +/- 0.2 micrograms/gm of

tissue). Suppression of hCG by progesterone occurred in a dose-response manner (r = -0.9100, p less than 0.01). Estradiol, an important **steroid modulator** of pituitary gonadotropins, did not significantly suppress the secretion of hCG, except in pharmacologic concentrations (10(-4)M), and physiologic concentrations of estradiol had no effect on the suppression of hCG by progesterone. These results suggest that the mechanism by which progesterone suppresses the secretion of hCG differs from the manner in which steroids modulate the secretion of pituitary gonadotropins.

L7 ANSWER 12 OF 12 MEDLINE
TI Fetal adrenal cortex.
AU Buster J E
SO CLINICAL OBSTETRICS AND GYNECOLOGY, (1980 Sep) 23 (3) 803-24. Ref: 31
Journal code: DFL; 0070014. ISSN: 0009-9201.
AB The fetal adrenal cortex is the central **steroid modulator** in the fetal placental complex. Its anatomic structure and physiology clearly identify it as a uniquely fetal organ that undergoes atrophy to a fraction of its intrauterine size after birth and assumes markedly different steroidogenic functions on the assumption of extrauterine life. Its importance as a regulator of maturation and parturition in normal gestation is just being understood. The fetal adrenal cortex no doubt plays major roles in the pathogenesis of some of the most important clinical problems currently faced in contemporary obstetrics. Continued research that provides a more complete understanding of this organ will serve as the major base for innovative diagnostic and therapeutic advancements of the future.